## REMARKS

CSA has been expanded and the double periods have been eliminated, as requested by the Examiner.

The rejection of claim 24 under 35 U.S.C. 112, first paragraph as failure to comply with the written description requirement is respectfully traversed. Since the same text appears on page 5, at lines 24-26, the written description requirement is clearly met. The Office Action did note that the specification provides no further details on specific compounds but it is respectfully submitted that there is no requirement to do so. A patent specification is directed to a person skilled in the art and such people would know what compounds have been found to be effective in the treatment of OSA or CSA. For example, the Hedner PCT Published application cited by the Examiner lists several such compounds. Withdrawal of this rejection is respectfully solicited.

The claims have been rejected under 35 U.S.C. 103 over Hedner in view of LaRoche. This rejection is respectfully traversed. For the Examiner's information, the U.S. application corresponding to the cited Hedner PCT case is application Serial Number 10/204,048 and the inventors are the same as in this application.

The Examiner's description of both the Hedner and LaRoche references need not be discussed since applicants respectfully take issue with the *sub silencio* rationale for combining these references. That rationale simply assumes there is a relationship between the compounds which suggests substitution for treating OSA. There is no basis for that assumption.

The antiepileptic drugs listed in LaRoche et al. are zonisamide, topiramate, felbamate, lamotrigine, tiagabine, levetiracetam, gabapentin and oxcarbamazepine. Their structures are illustrated in the annexed Formula Sheet, and it is evident that these drugs

lack a common structural element. In other words, their antiepileptic (or other) effect cannot be predicted from their structure.

With respect to mechanism of action, LaRoche teaches there is a highly variable and different pharmacological effect. These effects include sodium channel blockade, calcium channel blockade, potentiation of GABA activity and antagonism of glutamate. Gabapentin and levetiracetam have unknown pharmacological mechanisms or at least they are not specified in the cited publication. The figure on page 607 shows that the drugs exhibit independent and specific interaction with the listed neuroregulatory systems. More specifically, zonisamide and topiramate both exhibit effects on sodium and calcium channels whereas topiramate has additional effects on GABA and glutamate neurons.

The rejection is predicated on the assumption that because topiramate and zonisamide are antiepileptics and both exhibit effects on sodium and calcium channels implies that they can reasonably be expected to elicit similar effects in an entirely different indication such as, for instance, sleep apnea or sleep disordered breathing. No factual support for the assumption that a therapeutic effect shared by two drugs in one medical indication *ipso facto* permits the prediction of a parallel action in a second, unrelated medical indication has been provided.

Beyond the speculative assumption of common activity, there is no evidence suggesting that compounds that are therapeutically active in epilepsy in general also would have an effect in sleep apnea. Quite to the contrary, some have been described to have purely respiratory depressant effects and would be contra-indicated in sleep apnea.

For instance, compounds with GABA agonistic effects have long been known to exhibit respiratory depressant effect in various animal models (Hedner et al., *GABA-ergic mechanisms in central respiratory control in the anesthetized rat.* Naunyn Schmiedebergs Arch Pharmacol. 1981;317(4):315-20). The anticonvulsant vigabatrin may cause sleep apnea

according to Lambert and Bird (*Obstructive sleep apnoea following rapid weight gain secondary to treatment with vigabatrin (Sabril)*. Seizure, 1997 Jun;6(3):233-5). High dose gabapentin (referenced by LaRoche) induced respiratory depression and apnea in an adult patient which required intubation and artificial respiration (Spiller et al. *Massive gabapentin and presumptive quetiapine overdose*. Vet Hum Toxicol. 2002 Aug;44(4):243-4). Benzodiazepine receptors which are GABA receptor complex associated are also known to depress ventilation and may induce apnea. The antiepileptic clonazepam induces respiratory depressant effects similar to other benzodiazepines. The apnea index was increased suggesting more severe sleep apnea in a controlled study of bruxism patients (Saletu et al., *On the pharmacotherapy of sleep bruxism: placebo-controlled polysomnographic and psychometric studies with clonazepam*. Neuropsychobiology. 2005;51(4):214-25. Epub 2005 May 23). Two additional studies (Schuld et al., *Obstructive sleep apnea syndrome induced by clonazepam in a narcoleptic patient with REM-sleep-behavior disorder*. J Sleep Res. 1999 Dec;8(4):321-2) and (Berry et al., *Triazolam in patients with obstructive sleep apnea*. Am J Respir Crit Care Med. 1995 Feb;151(2 Pt 1):450-4) further supports this suggestion.

There is very little data in the literature dealing with respiratory effects of the zonisamide, topiramate, felbamate, lamotrigine, tiagabine or levetiracetam anticonvulsants listed in the LaRoche review. However, the anticonvulsant carbamazepine may upon toxic dosing cause apnea according to a case report (Stremski et al., *Pediatric carbamazepine intoxication*. Ann Emerg Med. 1995 May;25(5):624-30).

The Office Action notes that both topiramate and zonisamide act as anti-convulsants by way of blocking sodium as well as t-ticalcium channels. If it were known that blocking sodium and t-ticalcium channels was useful in the treatment of OSA, then it could be argued that it would be obvious to try topiramate and/or zonisamide for that indication. However, the inventors are not aware of any such knowledge in the art and

neither the references themselves nor the Office Action indicate any such teaching is known. It is known that topiramate is useful to treat OSA but there is nothing which indicates to a person skilled in the art, how or why it does so. Because of these considerations, there is nothing which allows the skilled person to reasonably predict that zonisamide would be useful in the treatment of OSA.

Even though the substitution assertion in the Office Action is based on an assumption which has no basis, it is possible to test the assertion. If the fact that both drugs are broad spectrum anti-convulsants and act by way of blocking sodium as well as t-ticalcium channels is predictive of OSA activity, then a person with OSA should react in the same way to both drugs.

In order to test this, the inventors clinically evaluated the effects in four patients consecutively exposed to both topiramate (50 mg b.i.d) and zonisamide (100 mg b.i.d). Shown in the Table below are results from the sleep study performed at steady state with treatment at 4 to 6 weeks after initiation of either therapy. The designation (+) indicates a case in which there was a reduction of the apnea-hypopnea index by more than 50% and (-) indicates a reduction of less than 50%.

| Patient number | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Zonisamide | + | + | + | - |
| Topiramate | - | - | + | + |

Three of the 4 patients responded to one drug but not the other. Two patients responded to zonisamide but not to topiramate while the opposite was found in one patient. The fourth patient responded to both therapies. This data clearly shows that effects of these two compounds are unique and that an effect with one of the compounds does not imply that the other agent is effective. It also shows that antiepileptic activity commonality does

not reasonably permit a prediction that zonisamide will be active because topiramate is active.

All of the foregoing demonstrates that zonisamide represents a novel, unpredictable, unobvious and unique therapeutic modality in sleep apnea.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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